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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US98/25992 <b>(22) International Filing Date:</b> 8 December 1998 (08.12.98)  <b>(30) Priority Data:</b> 60/067,960 8 December 1997 (08.12.97) US  <b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 60/067,960 (CIP) Filed on 8 December 1997 (08.12.97)  <b>(71) Applicant (for all designated States except US):</b> THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> BOGER, Dale, L. [US/US]; 2819 Via Posada, La Jolla, CA 92037 (US).  <b>(74) Agents:</b> LEWIS, Donald, G. et al.; The Scripps Research Institute, 10550 North Torrey Pines Road, TPC-8, La Jolla, CA 92037 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SYNTHESIS OF CC-1065/DUOCARMYCIN ANALOGS		
<b>(57) Abstract</b>  The dihydroindole C-ring found in CC-1065/duocarmycin analogs is formed by the 5- <i>exo-trig</i> radical cyclization of an aryl halide onto a tethered vinyl chloride forming with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization. The versatility of this approach is disclosed in the context of six CC-1065/duocarmycin analogs previously synthesized in this laboratory.		

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## SYNTHESIS OF CC-1065/DUOCARMYCIN ANALOGS

DescriptionTechnical Field:

The present invention relates to a method for the synthesis of the dihydroindole C-ring found in CC-1065 / duocarmycin analogs. More particularly, the invention  
5 comprises the 5-exo-trig radical cyclization of an aryl halide onto a tethered vinyl chloride forming the dihydroindole C-ring with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization. The versatility of this approach is examined in the context of six CC-1065 /  
10 duocarmycin analogs previously synthesized in this laboratory.

Background:

CC-1065 (1; Chidester et al. *J. Am. Chem. Soc.* 1981, 1-3, 7629) and the duocarmycins 2 (Ichimura et al. *J. Antibiot.*  
15 1990, 43, 1037) and 3 (Takahashi et al. *J. Antibiot.* 1988, 41, 1915; Yasuzawa et al. *Chem. Pharm. Bull.* 1995, 43, 378) are the parent members of a potent class of antitumor antibiotics that derive their biological properties through reversible, sequence selective alkylation of DNA (For a review of  
20 mechanistic aspects see: Boger, et al. *Angew. Chem., Int. Ed. Engl.* 1996, 35, 230).

Since their disclosure, synthetic efforts have focused on the natural products as well as a great number of rationally designed analogs (For a review of synthetic efforts see: Boger  
25 et al. *Chem. Rev.*, 1997, 97, 787). These analogs have served to define the fundamental principles underlying the relationships between structure, chemical reactivity and biological properties within this family, and have advanced the understanding of the origin of sequence selectivity and the  
30 catalysis of the DNA alkylation reaction by 1-3 (Boger et al. *J. Am. Chem. Soc.* 1997, 119, 4977; Boger et al. *J. Am. Chem.*

Soc. 1997, 119, 4987; Boger et al. *Biorg. Med. Chem.* 1997, 5, 263; Warpehoski et al. *J. Am. Chem. Soc.* 1994, 116, 7573; Warpehoski et al. *J. Am. Chem. Soc.* 1995, 117, 2951).

5 Common synthetic routes to many of the duocarmycin and CC-1065 analogs incorporate the same transformation via a four step procedure highlighted by an *in-situ* trap of a primary radical with TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical) followed by its reductive removal  
10 and conversion to the chloride as depicted for the synthesis of CBI (Boger et al. *J. Org. Chem.* 1995, 60, 1271) as illustrated in Figure 4.

It would be beneficial to have a more direct and higher yielding transformation to obtain the dihydroindole C-ring  
15 found in CC-1065 / duocarmycin analogs. What is needed, therefore, is an efficient and general method for the synthesis of the dihydroindole C-ring found in CC-1065 / duocarmycin analogs with less steps than the standard four step TEMPO procedure as described above.

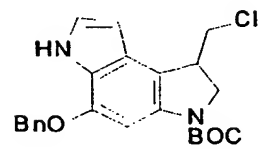
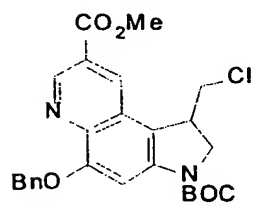
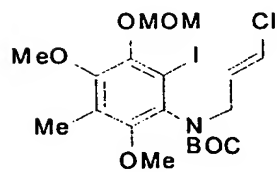
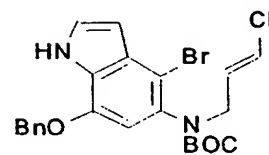
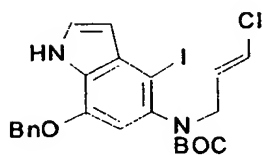
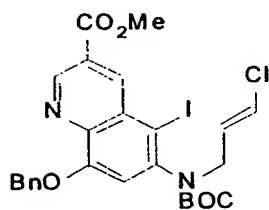
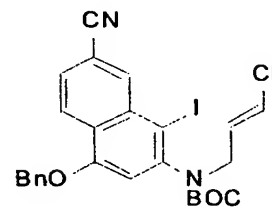
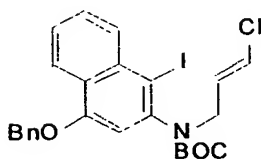
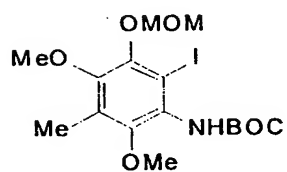
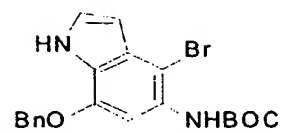
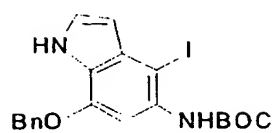
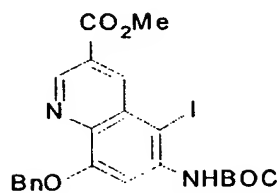
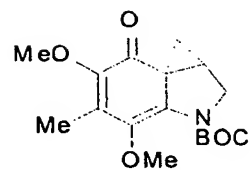
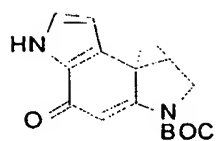
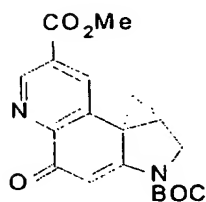
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#### Summary of the Invention:

One aspect of the invention is directed to a 2 step synthesis of the dihydroindole C-ring found in CC-1065 / duocarmycin analog. An aryl halide is alkylated with 1,3-  
25 dichloropropene and a catalytic amount of *n*-tetrabutylammonium iodide for forming a vinyl chloride. The vinyl chloride is then cyclized under conditions using tributyl tin hydride, catalytic AIBN and toluene as the solvent for forming the dihydroindole C-ring of the CC-1065/duocarmycin analog.

30

Another aspect of the invention is directed to the following compounds:





### Description of Figures:

Figure 1 shows CC-1065 (1) and the duocarmycins (2) and (3). The compounds are parent members of a potent class of antitumor antibiotics.

5 Figure 2 shows CBI (4) (5), CPyI (6), desmethyl-CPI (7), *iso*-CBI (8), and the mitomycin-hybrid (9) which are compounds of interest in this application.

Figure 3 shows the novel intramolecular aryl radical cyclization onto a tethered vinyl chloride to install the dihydroindole C ring with chlorine installed as a suitable  
10 leaving group for subsequent cyclopropane spirocyclization.

Figure 4 shows the standard four step procedure highlighted by an *in-situ* trap of a primary radical with TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical)  
15 followed by its reductive removal and conversion to the chloride as depicted for the synthesis of CBI.

Figure 5 illustrates the transformation from compound 10a to 12a and the subsequent formation of a cyclopropyl ring.

Figure 6 shows a table which illustrates the results of  
20 the two-step synthesis of 3-chloro-methylindolines with the following conditions: a NaH, 1,3-dichloropropene, DMF, 25 °C; b NaH, 1,3-dichloropropene, *n*Bu<sub>4</sub>NI, DMF, 25 °C; c AIBN (cat.), Bu<sub>3</sub>SnH, benzene, 60-75 °C; d AIBN (cat.), Bu<sub>3</sub>SnH, toluene, 90°C wherein each compound uses the same transformation as  
25 shown in Figure 6.



Detailed Description of the Invention

The invention is directed to a two-step transformation directed to the synthesis of 6 CC-1065/duocarmycin analogs using a novel intramolecular aryl radical cyclization onto a vinyl chloride to form the dihydroindole C-ring found in 6  
5 CC-1065/duocarmycin analogs. This transformation represents a potential two-step improvement to the synthetic route to many other analogs, which most recently incorporated the same transformation via a four step procedure highlighted by an in-  
10 situ trap of a primary radical with TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical) followed by its reductive removal and conversion to the chloride as depicted for the synthesis of CBI (Boger et al. *J. Org. Chem.* 1995, 60, 1271) as illustrated in Figure 4.

15 Patel et al. describes the synthesis of an analog named Oxa-duocarmycin SA which utilizes a novel intramolecular aryl radical cyclization onto a tethered vinyl chloride to install the dihydroindole C ring with chlorine installed as a suitable leaving group for subsequent cyclopropane spirocyclization as  
20 described in Figure 3.

Application of this improved two-step transformation to the synthetic routes reported for a number of the analogs synthesized in this laboratory would serve to establish the versatility of this approach to the synthesis of CC-1065 and duocarmycin  
25 analogs.

With this goal in mind, the C-ring construction for CBI (4; Boger et al. *J. Org. Chem.* 1995, 60, 1271, CCBI (5; Boger et al. *J. Org. Chem.* 1996, 61, 4894), CPyI (6), desmethyl-CPI (7), iso-CBI (8), and the mitomycin-hybrid (9) was investigated. The  
30 appropriately functionalized aryl halides (10a-g), which were obtained either through direct electrophilic halogenation (entries 1-5) or directed ortho metallation (entries 6 and 7) and halide quench, were alkylated with 1,3 dichloropropene to

complete the radical cyclization precursors (11a-g) in high yields. Treatment with  $\text{Bu}_3\text{SnH}$  and a catalytic amount of AIBN (AIBN = 2,2'-azobisisobutyronitrile) with heating in benzene or toluene very cleanly effected 5-exo-trig radical cyclization to form the 3-chloromethyl indoline C-ring present in each of the analogs (12a-g) as illustrated in Figure 6.

This two-step transformation works well with benzene, naphthalene, indole and quinoline derivatives, aryl iodides as well as aryl bromides, with little to no deterioration in the consistently high yields for both steps. Brief optimization efforts revealed that higher yields may sometimes be obtained with addition of  $n\text{-Bu}_4\text{NI}$  to the alkylation reaction, as well as substitution of toluene and higher reaction temperature for benzene. It was observed, as also noted by Patel et al. that deoxygenation of the solvent prior to radical cyclization may enhance both the rate and yield of the reaction.

In summary, this novel intramolecular aryl radical cyclization onto a vinyl chloride, as introduced by Patel, was successfully applied to the C-ring synthesis of 6 CC-1065/duocarmycin analogs. This application has effectively shortened the synthesis of each of these analogs by two steps. Clearly the versatility of this approach, combined with the high conversions for both steps, assure its use in future rational analog design in the CC-1065/duocarmycin family of antitumor antibiotics.

While a preferred form of the invention has been shown in the drawings and described, since variations in the preferred form will be apparent to those skilled in the art, the invention should not be construed as limited to the specific form shown and described, but instead is as set forth in the following claims.

#### EXPERIMENTAL PROTOCOLS

General  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra were recorded either on a Bruker AM-250, a Bruker AMX-400 or a Bruker AMX-500

spectrometer. Residual protic solvent  $\text{CHCl}_3$  ( $\delta_{\text{H}} = 7.26$  ppm,  $\delta_{\text{C}} = 77.0$ ),  $\text{d}_4$ -methanol ( $\delta_{\text{H}} = 3.30$  ppm,  $\delta_{\text{C}} = 49.0$ ) and  $\text{D}_2\text{O}$  ( $\delta_{\text{H}} = 4.80$  ppm,  $\delta_{\text{C}}$  (of  $\text{CH}_3\text{CN}$ ) = 1.7 ppm) or TMS ( $\delta_{\text{H}} = 0.00$  ppm) were used as internal reference. Coupling constants were measured in Hertz (Hz). HRMS were recorded using FAB method in a *m*-nitrobenzylalcohol (NBA) matrix doped with NaI or CsI. Infra-red spectra were recorded on a Perkin-Elmer FTIR 1620 spectrometer. Enantiomeric excess was determined by HPLC using a Daicel Chemical Industries CHIRALPAK AD column. Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel  $\text{F}_{254}$ ) and visualized by cerium molybdophosphate or ninhydrin. Diethyl ether, tetrahydrofuran (THF) and toluene ( $\text{PhCH}_3$ ) were distilled from sodium-benzophenone ketyl, dichloromethane (DCM) and acetonitrile from calcium hydride. Other solvents and reagents were purified by standard procedures if necessary.

**General Experimental Procedure for individual synthesis of 12a-g as shown in Figure 6:**

A solution of the aryl iodide (one of 10a-g as shown in Figure 6 obtained from the sources or conditions as described herein; aryl iodide is obtained from the following sources:) in anhydrous DMF (0.1M) at 0 °C was treated with NaH (2.0 equiv.) in small portions. The resulting suspension was stirred 15 min and treated with neat 1,3-dichloropropene (5.0 equiv) in a slow dropwise manner, followed by catalytic  $\text{Bu}_4\text{NI}$  (0.1 equiv.; *n*-tetrabutylammonium iodide). The reaction mixture was warmed to 25 °C and stirred for 12 h. The reaction mixture was quenched with the addition of 5% aqueous  $\text{NaHCO}_3$ , and the aqueous layer was extracted with EtOAc. The combined organic extracts were

washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude was purified by flash column chromatography. A solution of one of 11a-g in anhydrous benzene (0.1M; alternatively substitution of toluene and higher reaction temperature can optimize yield, due to higher temperatures) was treated with Bu<sub>3</sub>SnH (1.05 equiv.) and catalytic AIBN (0.1 equiv.) and deoxygenated with a stream of dry N<sub>2</sub> gas. The solution was heated to 80 °C for 2 h and concentrated *in vacuo*. The crude was purified by flash column chromatography to form one of compounds 12a-g.

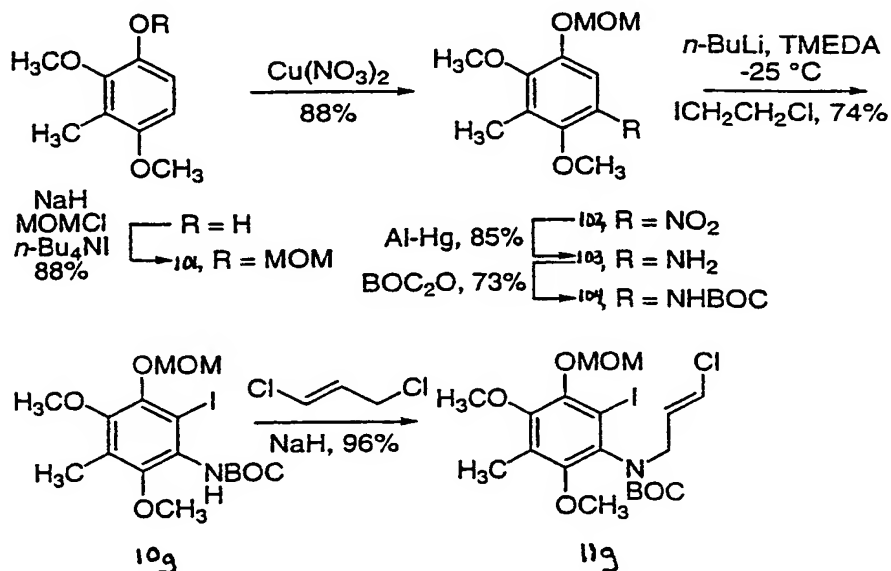
**Synthesis of cyclopropane via spirocyclization.** The chlorine group of the dihydroindole C-ring is installed as a suitable leaving group for cyclopropane spirocyclization. Methodologies for subsequent spirocyclization and further alkylation of the resultant cyclopropane C-ring system to the DNA portion of CC-1065 and the duocarmycins is well known in the art. A representative spirocyclization is accomplished via treatment of 12(a-g) with NaH (3 equiv, THF, 0 °C, 30 min) to provide (4-9; as shown in Figure 2). Similarly, acid-catalyzed deprotection of 12(a-g) (3N HCl-EtOAc, 25 °C, 20 min) followed by spirocyclization of the crude indoline hydrochloride salt upon exposure to 5% aqueous NaHCO<sub>3</sub>-THF (1:1, 25 °C, 1.5 h, 93%) can also provide (4-9; as shown in Figure 2).

#### **Synthesis of compounds 4-9 as shown in Figure 2**

A solution of 12(a-g; one of the compounds in Figure 6; obtained from the sources or conditions as described herein) (1.5 mg, 4.1 μmol) in tetrahydrofuran-dimethylformamide (3:1, 200 μL) at 0 °C under N<sub>2</sub> was treated with suspension of NaH (0.5 mg, 60% in an oil dispersion, 12 μmol, 3 equiv). The reaction mixture was allowed to stir at 0 °C and for 30 min

before the addition of pH 7 phosphate buffer (0.2 M, 250  $\mu$ L) and 2 mL of tetrahydrofuran. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. Chromatography ( $\text{SiO}_2$ , 20-30% Ethylacetate-hexane gradient elution) afforded (4-9; as shown in Figure 2):

Alternative Spyrocyclization: 12(a-g; one of the compounds) (5 mg, 1.37  $\mu$ mol) was treated with anhydrous 3N HCl-Ethylacetate (0.4 mL) at 24  $^\circ\text{C}$  for 20 min. The solvent was removed in vacuo to afford the crude, unstable amine hydrochloride. This residue was treated with 5% aqueous  $\text{NaHCO}_3$  (0.4 mL) and tetrahydrofuran (0.4 mL) at 24  $^\circ\text{C}$  under  $\text{N}_2$ , and the two phase mixture was stirred for 1.5 h (24  $^\circ\text{C}$ ). The reaction mixture was extracted with Ethylacetate (3 x 2 mL) and the combined extracts were washed with  $\text{H}_2\text{O}$  (2 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo. Chromatography ( $\text{SiO}_2$ , 10%  $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$ ) afforded (4-9; as shown in Figure 2).



**2,4-(Dimethoxy)-3-(methyl)-methoxymethyl phenyl ether (101).**

A solution of 2,4-(dimethoxy)-3-methylphenol (1.0 g, 5.95 mmol) in 60 mL of anhydrous DMF at 0 °C was treated with NaH (357 mg, 9.91 mmol) in several portions over 5 min. After 10 min, Bu<sub>4</sub>NI (219 mg, 0.60 mmol) was added followed by the dropwise addition of ClCH<sub>2</sub>OCH<sub>3</sub> (0.68 mL, 8.91 mmol). The reaction mixture was stirred at 25°C for 36 h before the reaction was quenched by the slow addition of 30 mL of H<sub>2</sub>O. The aqueous layer was extracted with EtOAc (3 ( 30 mL). The organic layers were combined, washed with 10% aqueous NaHCO<sub>3</sub> (50 mL) and H<sub>2</sub>O (4 ( 20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Flash chromatography (SiO<sub>2</sub>, 3 ( 10 cm, 10% EtOAc/hexane) provided **101** (1.11 g, 88%) as a light yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) δ 6.92 (d, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 1H), 5.13 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.50 (s, 3H), 2.13 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz) δ 153.5, 149.2, 144.3, 121.0, 114.4, 105.3, 96.0, 60.4, 56.0, 55.7, 8.9; IR (film) ν<sub>max</sub> 2937, 2833, 1595, 1487, 1440, 1420 cm<sup>-1</sup>; FABHRMS (NBA) *m/z* 212.1040 (C<sub>11</sub>H<sub>16</sub>O<sub>4</sub> requires 212.1049).

**2,4-(Dimethoxy)-3-(methyl)-5-(nitro)-methoxymethyl phenyl ether (102).**

A solution of **101** (1.11 g, 5.21 mmol) in 18 mL freshly distilled Ac<sub>2</sub>O at 0°C was treated with Cu(NO<sub>3</sub>)<sub>2</sub>•2.5 H<sub>2</sub>O (2.41 g, 10.4 mmol) in several portions over 5 min. The reaction mixture was stirred for 2 h at 0 °C, then 1 h at 25 °C before the reaction was poured over H<sub>2</sub>O (50 mL) and extracted with EtOAc (3 ( 30 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The crude light yellow oil (1.18 g, 88%) was carried on to the next transformation: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz) δ 7.54 (s, 1H), 5.18 (s, 2H), 3.87 (s,

3H), 3.81 (s, 3H), 3.48 (s, 3H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 62.5 MHz)  $\delta$  153.0, 147.8, 145.8, 138.9, 128.2, 110.5, 95.3, 61.8, 60.5, 56.2, 9.5; IR (film)  $\nu_{\text{max}}$  2942, 2829, 1522, 1481, 1344, 1280, 1246  $\text{cm}^{-1}$ ; FABHRMS (NBA)  $m/z$  258.0977 ( $\text{C}_{11}\text{H}_{15}\text{NO}_6 + \text{H}^+$  requires 258.0978).

**5-(Amino)-2,4-(dimethoxy)-3-(methyl)-methoxymethyl phenyl ether (103).**

A solution of 102 (1.18 g, 4.57 mmol) in 90 mL moist ether (8:2:1  $\text{Et}_2\text{O}:\text{EtOH}:\text{H}_2\text{O}$ ) was cooled to  $0^\circ\text{C}$ , and treated with freshly prepared Al-Hg (1.23 g Al, 45.7 mmol) in small 1 (1 cm pieces). The reaction mixture was stirred vigorously for 0.5 h at  $0^\circ\text{C}$ , then 1 h at  $25^\circ\text{C}$ . The reaction mixture was then filtered through Celite, and the Celite was washed thoroughly with  $\text{Et}_2\text{O}$  (5 (20 mL). The solution was then washed with saturated aqueous NaCl (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure to afford 103 (0.88 g, 85%) as a crude brown oil, which was immediately carried on to the next step:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  6.42 (s, 1H), 5.11 (s, 2H), 3.70 (s, 3H), 3.66 (s, 3H), 3.56 (m, 2H), 3.47 (s, 3H), 2.16 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  147.0, 140.4, 140.3, 135.8, 125.4, 102.0, 95.4, 60.6, 59.4, 56.0, 9.34; IR (film)  $\nu_{\text{max}}$  3446, 3359, 2935, 2826, 1617, 1492, 1358  $\text{cm}^{-1}$ ; ESIMS  $m/z$  228 ( $\text{C}_{11}\text{H}_{17}\text{NO}_4 + \text{H}^+$  requires 228).

**[N-(tert-Butyloxycarbonyl)amino]-2,4-(dimethoxy)-5-(methoxymethoxy)-3-methylbenzene (104).**

A solution of crude 102 (0.88 g, 3.85 mmol) in 40 mL anhydrous THF was treated with  $\text{BOC}_2\text{O}$  (1.73 g, 7.72 mmol) and the reaction mixture was warmed at reflux ( $65^\circ\text{C}$ ) for 18 h. The solvents were removed under reduced pressure, and flash chromatography ( $\text{SiO}_2$ , 3 (10 cm, 10%  $\text{EtOAc}$ /hexane) provided

pure **104** as a yellow oil (0.96g, 76%):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz)  $\delta$  7.72 (br s, 1H), 6.86 (br s, 1H), 5.18 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 3.51 (s, 3H), 2.19 (s, 3H), 1.50 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  152.7, 146.4, 143.6, 141.6, 127.8, 124.8, 105.3, 95.5, 80.4, 60.5, 60.4, 56.4, 28.3, 9.5; IR (film)  $\nu_{\text{max}}$  3437, 3341, 2977, 2935, 1731, 1519, 1454, 1422, 1397  $\text{cm}^{-1}$ ; FABHRMS (NBA/CsI)  $m/z$  460.0723 ( $\text{C}_{16}\text{H}_{25}\text{NO}_6$  +  $\text{Cs}^+$  requires 460.0736).

[*N*-(*tert*-Butyloxycarbonyl)amino]-2,4-(dimethoxy)-6-(iodo)-5-(methoxymethoxy)-3-methyl benzene (**10g**). A solution of **104** (0.55 g, 1.67 mmol) in 6.6 mL anhydrous THF was cooled to  $-25^\circ\text{C}$  and treated with TMEDA (0.94 mL, 6.18 mmol) followed by *n*-BuLi (2.5 mL of a 2.5 M solution in hexane, 6.18 mmol) in a slow dropwise manner. The resulting gold solution stirred for 2 h at  $-25^\circ\text{C}$ . The reaction mixture was treated with 1-chloro-2-iodoethane (0.45 mL, 6.18 mmol) and stirred for 15 min at  $25^\circ\text{C}$ . The reaction was diluted with  $\text{H}_2\text{O}$  (50 mL) and extracted with  $\text{Et}_2\text{O}$  (3 ( 30 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. Flash chromatography ( $\text{SiO}_2$ , 2.5 ( 10 cm, 20% EtOAc/hexane) yielded **11g** (560 mg, 74%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  5.99 (br s, 1H), 5.10 (s, 2H), 3.75 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 2.17 (s, 3H), 1.49 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  153.6, 151.8, 150.5, 146.9, 129.3, 126.7, 99.1, 95.8, 80.6, 60.5, 60.3, 58.5, 28.3, 9.8; IR (film)  $\nu_{\text{max}}$  3321, 2975, 2936, 1722, 1485, 1455, 1390  $\text{cm}^{-1}$ ; FABHRMS (NBA/CsI)  $m/z$  585.9688 ( $\text{C}_{16}\text{H}_{24}\text{INO}_6$  +  $\text{Cs}^+$  requires 585.9703).

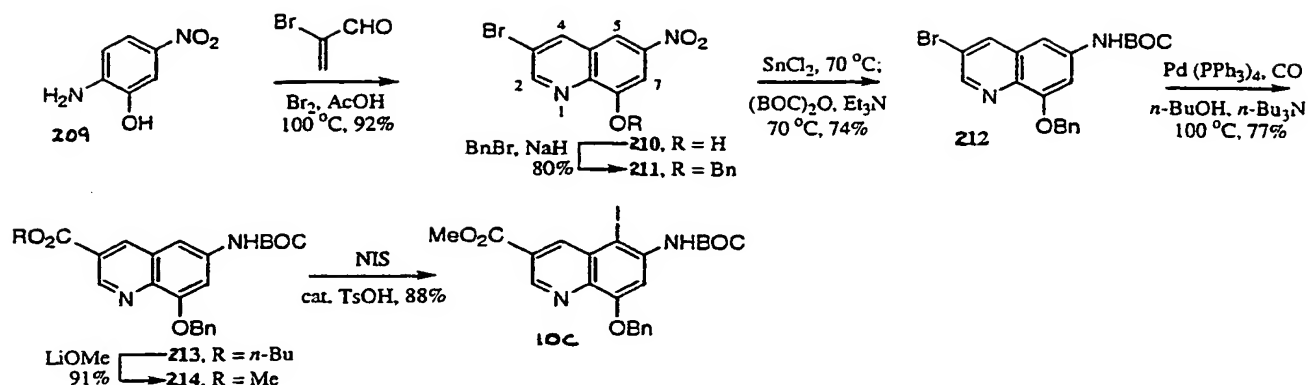
[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)amino]-2,4-(dimethoxy)-6-(iodo)-5-(methoxymethoxy)-3-methylbenzene



(11g).

A solution of 10g (0.610 g, 1.34 mmol) in 13.4 mL anhydrous DMF was cooled to 0 (C, and treated with NaH (60% dispersion in oil, 121 mg, 4.03 mmol) in small portions. The resulting suspension was stirred for 15 min and treated with neat 1,3-dichloropropene (0.52 mL, 5.5 mmol) in a slow dropwise manner, followed by catalytic *n*-Bu<sub>4</sub>NI (50.0 mg, 0.13 mmol). The reaction mixture was warmed to 25 (C and stirred for 3 h. The reaction mixture was quenched with the addition of saturated aqueous NaHCO<sub>3</sub> (50mL), and the aqueous layer was extracted with EtOAc (3 ( 30 mL). The combined organic extracts were washed with H<sub>2</sub>O (4 ( 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Flash chromatography (SiO<sub>2</sub>, 3 ( 10 cm, 0-20% EtOAc/hexane gradient) yielded 11g (0.681 g, 96%) as a colorless mixture of rotamers: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) 2:1 rotamers δ 6.15-6.03 (m, 1H), 6.00-5.90 (m, 1H), 5.11-5.03 (m, 2H), 4.17-3.87 (m, 2H), 3.77 and 3.74 (s, 3H), 3.65 and 3.63 (s, 3H), 3.627 and 3.622 (s, 3H), 2.14 and 2.13 (s, 3H), 1.50 and 1.34 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) rotamers δ 153.65 and 153.62, 152.8 and 152.1, 151.0 and 150.7, 147.0 and 146.7, 134.5 and 134.0, 129.5 and 129.0, 127.0 and 126.7, 121.0 and 120.6, 99.0, 97.7 and 97.3, 80.8 and 80.6, 60.5 and 60.4, 60.3 and 60.2, 58.5 and 58.4, 50.4, 48.8, 28.3 and 28.2, 9.9; IR (film) ν<sub>max</sub> 2973, 2936, 1704, 1456, 1366 cm<sup>-1</sup>; FABHRMS (NBA/CsI) *m/z* 659.9655 (C<sub>19</sub>H<sub>27</sub>ClINO<sub>6</sub> + Cs<sup>+</sup> requires 659.9626).

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### 3-Bromo-8-hydroxy-6-nitroquinoline (210).

A solution of 2-bromoacrolein (5 g, 37.0 mmol, 1 equiv) in 110 mL glacial acetic acid at  $25^\circ\text{C}$  was titrated to the appearance of a faint reddish color with bromine (ca. 5.9 g, 37.0 mmol, 1 equiv). 2-Hydroxy-4-nitroaniline (**209**, 5.7 g, 37.0 mmol, 1 equiv) was added, and the solution was gradually heated to  $100^\circ\text{C}$ . The solution was cooled to  $25^\circ\text{C}$  after one hour. Filtering and neutralization of the precipitate with 1 M sodium phosphate buffer (pH 7,  $\text{Na}_2\text{HPO}_4\text{-NaH}_2\text{PO}_4$ ) afforded 9.2 g (9.95 g theoretical, 92%) of **210** as a light yellow solid: mp  $240\text{--}241^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.93 (d,  $J = 2.0$  Hz, 1H), 8.50 (d,  $J = 2.0$  Hz, 1H), 8.23 (d,  $J = 2.2$  Hz, 1H), 8.18 (s, 1H), 7.92 (s,  $J = 2.3$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{DMSO}$ , 62.5 MHz)  $\delta$  155.1, 152.1, 146.3, 139.5, 139.1, 128.7, 119.1, 113.5, 105.1; IR (film) ( $\text{max}$  3408 (br), 3089, 1587, 1553, 1519, 1476, 1389, 1350, 1297, 1263, 1210, 1133, 1079, 929, 931, 839, 804, 734, 633  $\text{cm}^{-1}$ ; ESIMS  $m/z$  269 ( $\text{M} + \text{H}^+$ ,  $\text{C}_9\text{H}_7\text{BrO}$  requires 269); Anal. Calcd for  $\text{C}_9\text{H}_7\text{BrO}$ : C, 40.18; H, 1.87; N, 10.41. Found: C, 40.21; H, 1.91; N, 9.98.

### 8-(Benzyloxy)-3-bromo-6-nitroquinoline (211). A solution of **210**

(13.7 g, 51 mmol, 1 equiv) in anhydrous DMF (150 mL)

was cooled to 4 °C under nitrogen and treated with KI (1.7 g, 10 mmol, 0.2 equiv) and sodium hydride (60% dispersion in oil, 2.24 g, 56 mmol, 1.1 equiv). Benzyl bromide (7.3 mL, 6.1 mmol, 1.2 equiv) was added after 30 min and the reaction was allowed to warm to 25 °C. After 24 h, the reaction volume was reduced by one-third in vacuo and EtOAc (200 mL) was added. The reaction mixture was poured on H<sub>2</sub>O (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Flash chromatography (SiO<sub>2</sub>, 5.5 × 20 cm, 50-100% CH<sub>2</sub>Cl<sub>2</sub>-hexane) afforded **211** (15.63 g, 18.32 g theoretical, 85%) as a yellow solid: mp 170 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 9.06 (d, *J* = 2.2 Hz, 1H), 8.44 (d, *J* = 2.2 Hz, 1H), 8.25 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.52 (app d, *J* = 7.4 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 5.47 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz) δ 155.4, 153.3, 146.4, 140.3, 138.8, 135.0, 128.7 (2C), 128.6, 128.4 (2C), 127.5, 119.9, 115.1, 103.3, 71.4; IR (film) (max 3082, 3055, 2933, 2871, 1609, 1567, 1519, 1476, 1450, 1375, 1338, 1311, 1252, 1135, 1093, 976, 912, 842, 741 cm<sup>-1</sup>; FABHRMS (NBA/NaI) *m/z* 359.0040 (*M* + H<sup>+</sup>, C<sub>16</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>3</sub> requires 359.0031). Anal. Calcd for C<sub>16</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 53.50; H, 3.09; N, 7.80. Found: C, 53.81; H, 3.23; N, 7.48.

**8-(Benzyloxy)-3-bromo-6-*N*-(tert-butyloxycarbonyl)aminoquinoline (212).** A solution of **211** (200 mg, 0.56 mmol, 1 equiv) in EtOAc (1.1 mL) at 25 °C was treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (628 mg, 2.78 mmol, 5 equiv). The reaction mixture was heated to 70 °C under nitrogen until an orange slurry formed (ca. 0.5 h). After cooling to 25 °C, the reaction mixture was poured on ice and made basic with 1N NaOH. The aqueous layer was filtered and extracted with EtOAc (3 × 15 mL). The combined organic layers were treated with saturated aqueous NaCl (1 × 10 mL),

dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The yellow solid was placed under vacuum for 0.5h and then dissolved in anhydrous dioxane (5 mL) and treated with di-*tert*-butyl dicarbonate (490 mg, 2.25 mmol, 4.0 equiv) and triethylamine (156  $\mu\text{L}$ , 1.12 mmol, 2.0 equiv). The reaction mixture was warmed to  $70^\circ\text{C}$  under argon for one day. After cooling, the solvent was removed in *vacuo*. Chromatography ( $\text{SiO}_2$ , 3 (13 cm, 25% EtOAc-hexane) afforded **212** (179 mg, 240 mg theoretical, 74%) as a light yellow solid: mp 162 (C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  8.77 (d,  $J$  = 2.0 Hz, 1H), 8.13 (d,  $J$  = 2.5 Hz, 1H), 7.47 (app d,  $J$  = 7.5 Hz, 2H), 7.42 (d,  $J$  = 2.0 Hz, 1H), 7.35 (m, 2H), 7.28 (m, 1H), 7.01 (d,  $J$  = 2.0 Hz, 1H), 6.61 (s, 1H), 5.37 (s, 2H), 1.51 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  154.9, 152.4, 148.3, 137.9, 136.3, 136.2, 135.4, 131.0, 128.6 (2C), 128.0, 127.3 (2C), 118.6, 104.7, 103.6, 81.1, 70.9, 28.3 (3C); IR (film) ( $\text{max}$  3354, 2971, 2919, 1807, 1766, 1724, 1621, 1450, 1367, 1310, 1253, 1217, 1160, 1123, 1061, 843, 771, 699, 657  $\text{cm}^{-1}$ ; FABHRMS (NBA/CsI)  $m/z$  429.0825 ( $\text{M} + \text{H}^+$ ,  $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{O}_3$  requires 429.0814).

***n*-Butyl 8-(benzyloxy)-6-*N*-(*tert*-butyloxycarbonyl)aminoquinoline-3-carboxylate (213).**

A solution of **212** (4.4 g, 10.1 mmol, 1 equiv) in 85 mL *n*-BuOH was cooled to  $-78^\circ\text{C}$  and degassed under vacuum.  $\text{Pd}(\text{PPh}_3)_4$  (1.2g, 1.0 mmol, 0.1 equiv) and *n*-Bu<sub>3</sub>N (2.9 mL, 12.1 mmol, 1.2 equiv) were added and the solution was purged with nitrogen. The reaction mixture was then flushed with carbon monoxide and then slowly heated to  $100^\circ\text{C}$  under a CO atmosphere. Upon complete reaction (ca. 12 h), 50 mL  $\text{H}_2\text{O}$  and 50 mL saturated aqueous  $\text{NH}_4\text{Cl}$  were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 (50 mL). The combined organic layers were washed with saturated aqueous NaCl (1 (40 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and

concentrated. Chromatography (SiO<sub>2</sub>, 5.5 ( 20 cm, 25% EtOAc-hexane) afforded **213** (3.55 g, 4.55 g theoretical, 78%) as a yellow solid: mp 135-136 (C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 9.31 (d, *J* = 2.0 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.49 (app d, *J* = 7.4 Hz, 2H), 7.35 (app t, *J* = 7.2 Hz, 2H), 7.29 (m, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 6.64 (br s, 1H), 5.39 (s, 2H), 4.38 (t, *J* = 6.6 Hz, 2H), 1.78 (m, 2H), 1.52 (s, 9H), 1.49 (m, 2H, buried under 1.52 ppm), 0.98 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (acetone d<sub>6</sub>, 100 MHz) δ 165.7, 155.7, 153.5, 146.8, 139.8, 139.5, 137.8, 137.7, 129.5, 129.1 (2C), 128.6, 128.4 (2C), 124.8, 107.1, 106.9, 80.4, 71.2, 65.5, 31.3, 28.3 (3C), 19.8, 13.9. IR (film) (max 3222, 3049, 2958, 2930, 2876, 1717, 1617, 1544, 1503, 1430, 1362, 1271, 1239, 1157, 1065 cm<sup>-1</sup>; FABHRMS (NBA/CsI) *m/z* 451.2249 (M + H<sup>+</sup>, C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> requires 451.2233).

**Methyl-8-(benzyloxy)-6-N-(tert-butyloxycarbonyl)aminoquinoline-3-carboxylate (214)**. A solution of **213** (2.9g, 6.4 mmol, 1.0 equiv) in 70 mL MeOH was cooled to 4 (C under nitrogen and treated with LiOMe (275 mg, 7.1 mmol, 1.1 equiv). The reaction mixture was allowed to warm to 25 (C after 20 min. Upon complete reaction (ca. 1.5 h), 100 mL H<sub>2</sub>O was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 ( 30 mL). The organic layers were combined, washed with saturated aqueous NaCl (1 ( 30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography (SiO<sub>2</sub>, 5 ( 19 cm, 25 - 30% EtOAc-hexane) afforded **214** (2.39 g, 2.63 g theoretical, 91%) as a yellow solid: mp 173-174 (C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 9.29 (d, *J* = 2.0 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.45 (m, 2H), 7.30 (m, 2H), 7.25 (m, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.85 (s, 1H), 5.36 (s, 2H), 3.98 (s, 3H), 1.50 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 165.9, 154.6, 152.6, 146.9, 138.6, 137.9, 137.8, 136.0,

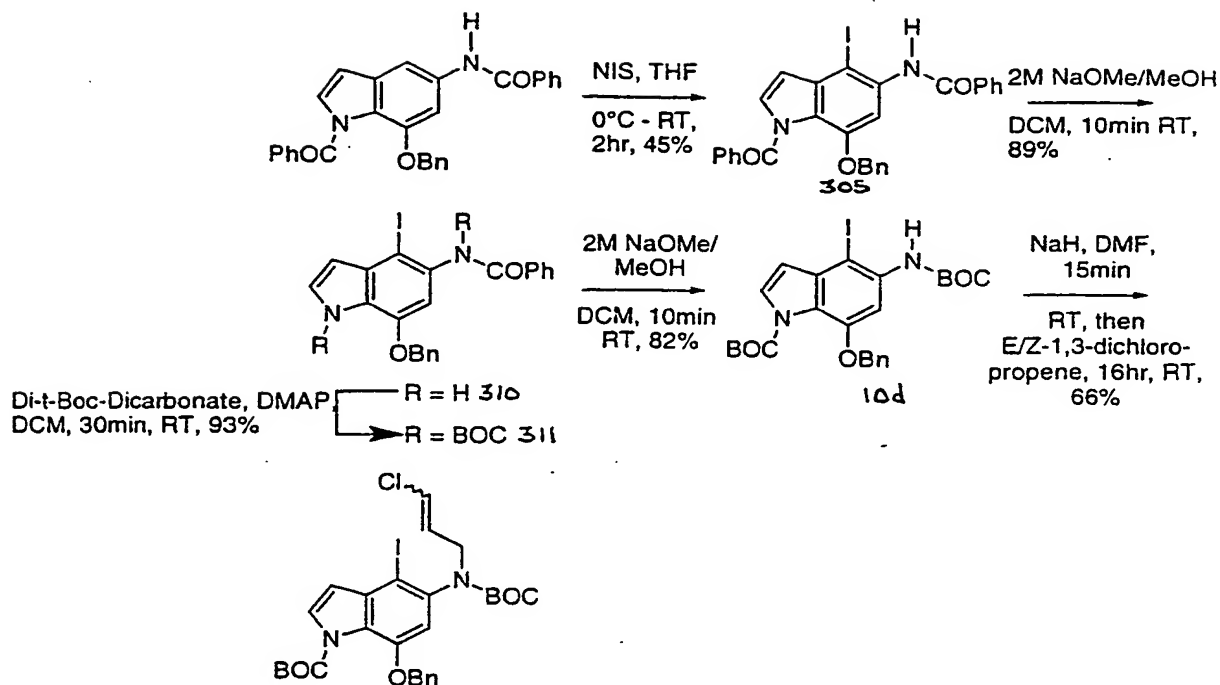
128.5, 128.4 (2C), 127.9, 127.3 (2C), 123.8, 106.5, 105.5, 80.8, 70.8, 52.4, 28.2 (3C); IR (film) ( $\text{max}$  3333, 3241, 2974, 1723, 1621, 1580, 1539, 1497, 1431, 1390, 1364, 1277, 1231, 1164, 1126, 1103, 1062, 1000, 882, 846, 795, 749, 697, 662  $\text{cm}^{-1}$ ; FABHRMS (NBA/CsI)  $m/z$  409.1773 ( $M + H^+$ ,  $C_{23}H_{24}N_2O_5$  requires 409.1763).

**Methyl 8-(benzyloxy)-6-[N-(tert-butyloxycarbonyl)amino]-5-iodoquinoline-3-carboxylate (10c).**

A solution of **214** (2.13 g, 5.2 mmol, 1 equiv) in 85 mL of a 1:1 mixture of THF-CH<sub>3</sub>OH was cooled to 4 °C and treated with 40 mg TsOH (or H<sub>2</sub>SO<sub>4</sub>) in 0.5 mL THF. N-Iodosuccinimide (1.4 g, 6.2 mmol, 1.2 equiv) in 10 mL THF was then slowly added over 10 min. After 1.5 h, the reaction mixture was warmed to 25 °C and then stirred 45 h. Upon complete reaction, 100 mL saturated aqueous NaHCO<sub>3</sub>, 100 mL Et<sub>2</sub>O, and 100 mL H<sub>2</sub>O were added. The organic layer was separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 ( 50 mL) and EtOAc (1 ( 50 mL). The organic layers were combined, washed with saturated aqueous NaHCO<sub>3</sub> (1 ( 50 mL) and saturated aqueous NaCl (1 ( 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Chromatography (SiO<sub>2</sub>, 5 ( 19 cm, hexanes then 30% EtOAc-hexane) provided **10c** (2.34 g, 2.78 g theoretical, 84%, typically 80-88%) as a yellow solid: mp 182-183 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  9.27 (d,  $J$  = 1.9 Hz, 1H), 8.96 (d,  $J$  = 1.9 Hz, 1H), 8.40 (s, 1H), 7.58 (m, 2H), 7.36 (m, 2H), 7.27 (m, 1H), 7.26 (s, 1H), 5.43 (s, 2H), 4.01 (s, 3H), 1.55 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 62.5 MHz)  $\delta$  165.4, 155.0, 152.3, 147.6, 141.9, 139.8, 139.7, 135.8, 129.6, 128.5 (2C), 128.1, 128.0 (2C), 125.1, 105.6, 81.7, 78.4, 71.1, 52.6, 28.2 (3C); IR (film) ( $\text{max}$  3384, 2974, 1723, 1595, 1554, 1498, 1431, 1400, 1359, 1328, 1262, 1226, 1149, 995, 754  $\text{cm}^{-1}$ ; FABHRMS (NBA/CsI)  $m/z$  535.0743 ( $M + H^+$ ,  $C_{23}H_{23}IN_2O_5$  requires

-19-

535.0730).



11d

# **N<sup>5</sup>,1-Dibenzoyl-5-amino-7-(benzyloxy)-4-iodoindole (305).**

The above indole (118mg, 0.26mmol) was stirred in THF (1mL) and toluenesulfonic acid (26mg, 0.13mmol) was added. The solution was cooled to 0°C and N-iodosuccinimide (71mg, 0.312mmol) in THF (1mL) was added. The reaction was allowed to warm to 25°C over 1 hr. After 16hr, a further portion of N-iodosuccinimide (15mg, 0.065mmol) was added and the reaction was stirred for a further 24hr. Saturated sodium bicarbonate solution (1mL) and water (4mL) were then added and the resulting mixture was extracted with chloroform (3 x 5mL). The organic layers were combined, dried (MgSO<sub>4</sub>) and volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (silica, ethyl acetate/hexane 3:7, 2.5 x 15cm) and crystallized from ethyl acetate to give the expected product (305) as a yellow solid (67mg, 45%); <sup>1</sup>H NMR

$\delta$ (ppm) ( $\text{CDCl}_3$ ) 8.15 (s, 1H, NH), 7.99 (d, 2H  $J$  = Hz), 7.64 (d, 2H,  $J$  = Hz), 7.58-7.47 (m, 4H, ArH), 7.30-7.17 (m, 5H, ArH), 6.58 (d, 1H,  $J$  = 3.6Hz), 4.92 (s, 2H).  $^{13}\text{C}$  NMR  $\delta$ (ppm) 168, 165.5, 147.3, 136.2, 135.8, 134.9, 134.7, 134.1, 132.2, 132.1, 129.8, 129.6, 129.5, 129.0, 128.4, 128.3, 128.2, 127.8, 127.7, 127.1, 127.0, 122.4, 110.6, 102.1, 71.9, 70.6 IR (neat)  $\nu_{\text{max}}$  3058, 1703, 1678, 1598, 1332, 1279, 1237, 695  $\text{cm}^{-1}$  Mass Spectrum (FAB, NAB/CsI) 705 ( $\text{M}^+ + \text{Cs}^+$ ) .

**$\text{N}^5$ -Benzoyl-5-amino-7-(benzyloxy)-4-iodoindole (310).**

The above iodo-compound (305) (193mg, 0.34mmol) was stirred in dichloromethane (10mL). Sodium methoxide in methanol (0.523mL, 1.04mmol) was added and the solution was stirred at RT for 10 min. Water (50mL) and ethyl acetate (50mL) were added and organic layer was separated, dried ( $\text{MgSO}_4$ ) and evaporated to give the crude product. Chromatography (2 x 15cm  $\text{SiO}_2$ , ethyl acetate/hexanes 1:3) gave the pure compound (142mg, 89%),  $R_f$  0.2 ( $\text{SiO}_2$ , ethyl acetate/hexanes 1:3) as a colourless solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.61 (s, 1H, NH), 8.31 (s, 1H, NH), 8.05 (s, 1H), 8.00 (d, 1H,  $J$  = 6.8Hz), 7.53 (m, 5H), 7.37 (m, 3H), 7.21 (dd, 1H,  $J$  = 2.8, 1.4Hz), 6.43 (dd, 1H,  $J$  = 2.7, 1.2Hz), 5.28 (s, 2H); IR (neat)  $\nu_{\text{max}}$  3290, 3010, 1658, 1573, 1535, 1355  $\text{cm}^{-1}$ ; FABHRMS (NBA-CsI)  $m/z$  600.9408. ( $\text{M} + \text{Cs}^+$ ,  $\text{C}_{22}\text{H}_{17}\text{IN}_2\text{O}_2$  requires 600.9389).

**$\text{N}^5$ -Benzoyl- $\text{N}^5$ ,1-di-(tert-butoxycarbonyl)-5-amino-7-(benzyloxy)-4-iodoindole (311).**

Di-tert-butyl dicarbonate (687mg, 3.16mmol) and DMAP (128mg, 1.04mmol) were added to a stirred solution of compound 310 (255mg, 0.54mmol) in dichloromethane (6mL). After 30min at RT the solution was directly subjected to chromatography (2 x 15cm  $\text{SiO}_2$ , ethyl acetate/hexane 1:4) to give the pure product



(390mg, 93%) as a colorless oil (Rf 0.80, SiO<sub>2</sub>, ethyl acetate/hexane 1:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) 7.81 (d, 2H, J = 6.9Hz), 7.55 (d, 1H, J = 3.6Hz), 7.45 (m, 5H), 7.31 (m, 3H), 6.82 (s, 1H), 6.57 (d, 1H, J = 3.6Hz), 5.15 (s, 2H), 1.47 (s, 9H), 1.22 (s, 9H); FABHRMS (NBA-CsI) m/z 801.0402 (M + Cs<sup>+</sup>, C<sub>32</sub>H<sub>33</sub>IN<sub>2</sub>O<sub>6</sub> requires 801.0438).

**N<sup>5</sup>,1-Di-(tert-butoxycarbonyl)-5-amino-7-(benzyloxy)-4-iodoindole (10d).**

Sodium methoxide in methanol (2M, 0.224mL, 0.44mmol) was added to a stirred solution of compound (311) (150mg, 0.22mmol) in dichloromethane (5mL). After 10 min at RT, water (25mL) and ethyl acetate (25mL) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (25mL) and the combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. Chromatography (2 x 15cm SiO<sub>2</sub>, gradient elution ethyl acetate/hexanes 1:9 to ethyl acetate/hexanes 1:3) gave the pure compound (102mg, 82%), Rf 0.8 (SiO<sub>2</sub>, ethyl acetate/hexanes 1:3) as a colourless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) 7.83 (br s, 1H, NH), 8.00 (d, 1H, J = 6.8Hz), 7.53 (m, 3H (1H + 2H), 7.37 (m, 3H), 6.84 (br s, 1H), 6.45 (d, 1H, J = 3.4Hz), 5.21 (s, 2H), 1.54 (s, 9H), 1.45 (s, 9H); IR (neat)  $\nu_{\max}$  3395, 2977, 1759, 1727, 1603, 1577, 1517, 1367, 1346, 1228, 1154, 1111 cm<sup>-1</sup>; FABHRMS (NBA-CsI) m/z 697.0176 (M + Cs<sup>+</sup>, C<sub>25</sub>H<sub>29</sub>IN<sub>2</sub>O<sub>5</sub> requires 697.0176).

**N<sup>5</sup>-(3-Chloro-2-propen-1-yl)-N<sup>5</sup>,1-di-((tert-butyloxy)carbonyl)-5-amino-7-(benzyloxy)-4-iodoindole (11d).**

Sodium hydride (22mg, 0.54mmol, 3eq, 60% dispersion) was added to a stirred solution of compound (10d) (100mg, 0.18mmol) in DMF (5mL). After 15 min at RT, E/Z-1,3-dichloropropene (0.025mL, 0.27mmol) was added. The

solution was stirred at Rt for 1hr. Water (50mL) and ethyl acetate (50mL) were then added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (50mL) and the combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated. Chromatography (2 x 15cm  $\text{SiO}_2$ , ethyl acetate/hexanes 1:9) gave the pure compound (75.4mg, 66%) as a mixture of E and Z isomers:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) major rotamer 7.47 (br s, 1H), 7.36 (m, 5H), 6.53 (m, 1H), 6.00 (m, 2H), 5.17 (s, 2H), 4.51 (m, 1H), 4.11 (m, 1H), 1.54 (s, 9H), 1.25 (s, 9H); IR (neat)  $\nu_{\text{max}}$  2976, 1759, 1701, 1630, 1570, 1367, 1157  $\text{cm}^{-1}$ ; FABHRMS (NBA- $\text{CsI}$ )  $m/z$  771.0125 ( $\text{M} + \text{Cs}^+$ ,  $\text{C}_{28}\text{H}_{32}\text{ClIN}_2\text{O}_5$  requires 771.0099)

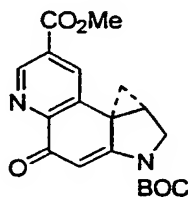
What is claimed:

1. A method for the synthesis of a dihydroindole C-ring of a CC-1065 / duocarmycin analog wherein the method comprises the steps of:

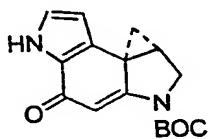
Step A: alkylating an aryl halide with 1,3-dichloropropene and a catalytic amount of *n*-tetrabutylammonium iodide for forming a vinyl chloride; then

Step B: cyclizing the vinyl chloride of said step A under conditions using tributyltin hydride, catalytic AIBN and toluene as the solvent for forming the dihydroindole C-ring of the CC-1065 / duocarmycin analog.

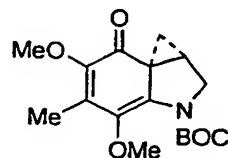
2. A compound represented by the following structure:



3. A compound represented by the following structure:

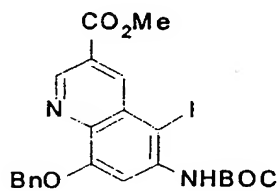


4. A compound represented by the following structure:

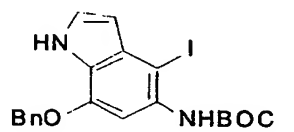


5. A compound represented by the following structure:

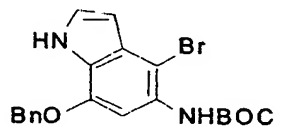
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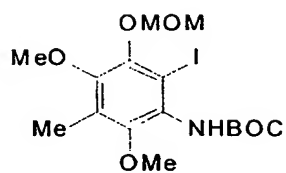
6. A compound represented by the following structure:



- 10 7. A compound represented by the following structure:

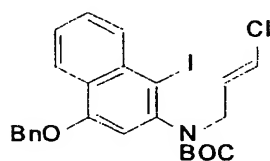


8. A compound represented by the following structure:



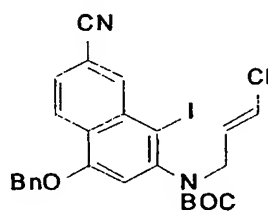
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9. A compound represented by the following structure:

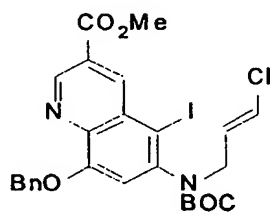


10. A compound represented by the following structure:

10

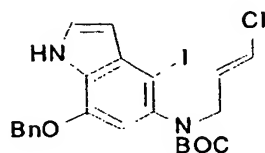


11. A compound represented by the following structure:

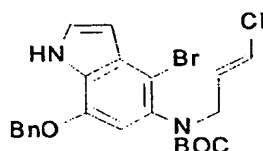


- 26 -

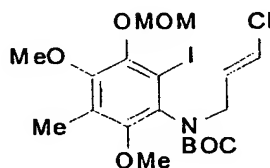
12. A compound represented by the following structure:



5 13. A compound represented by the following structure:

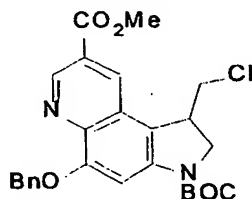


14. A compound represented by the following structure:



10

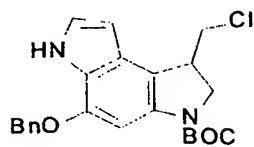
15. A compound represented by the following structure:



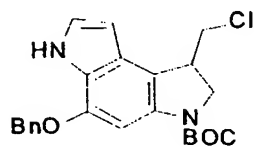
16. A compound represented by the following structure:

15

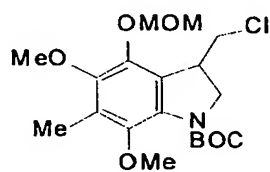
- 27 -



17. A compound represented by the following structure:



5 18. A compound represented by the following structure:



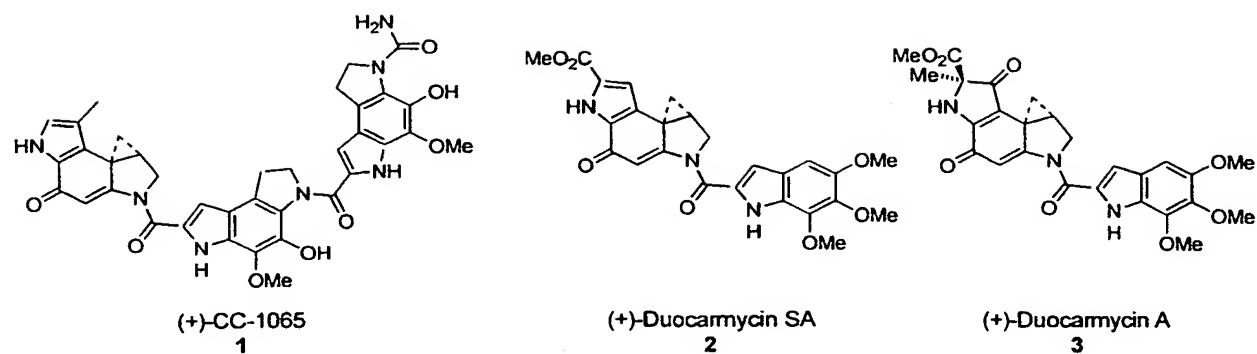


FIGURE 1

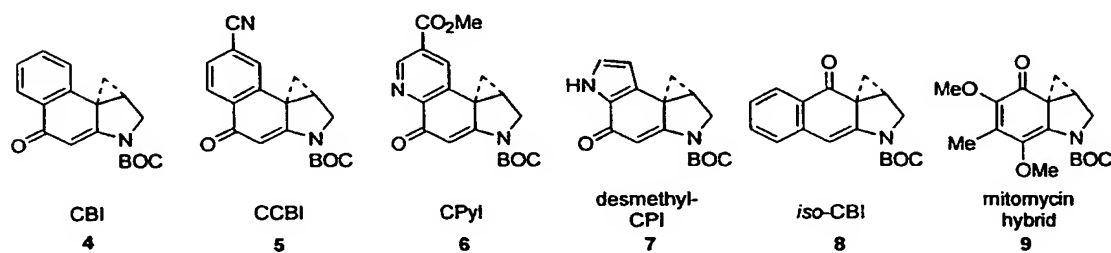


FIGURE 2

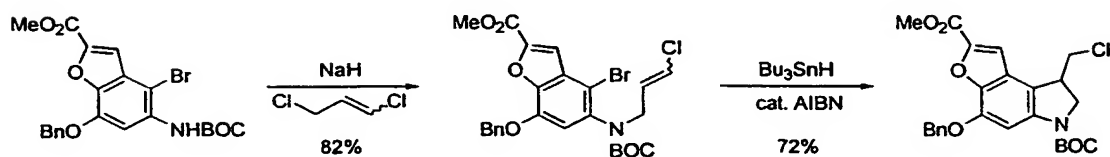


FIGURE 3



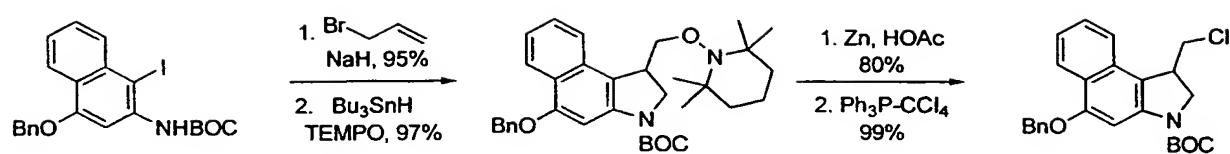


FIGURE 4

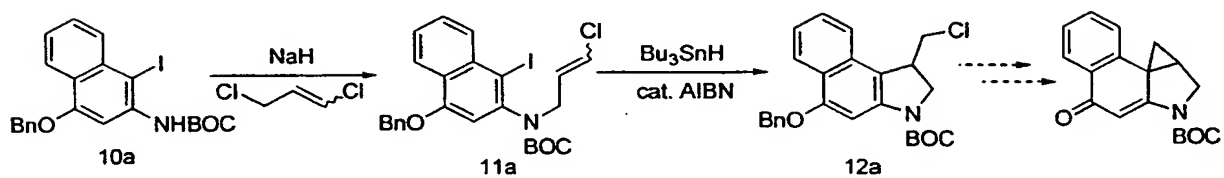


FIGURE 5

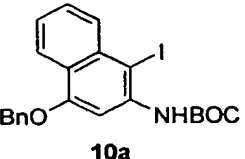


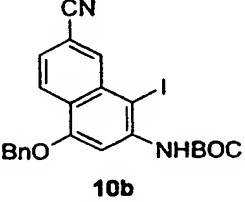
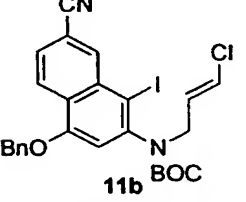
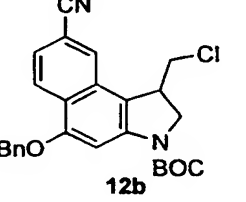
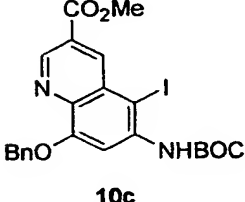
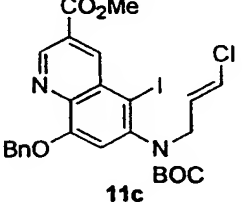
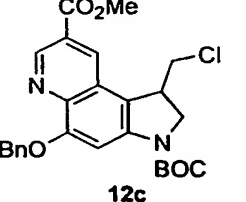
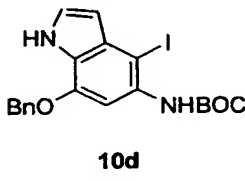
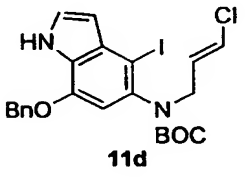
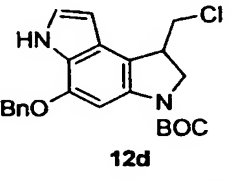
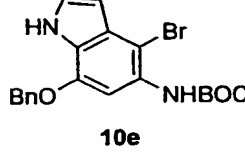
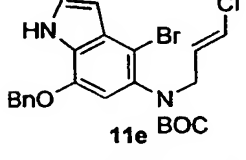
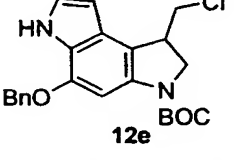
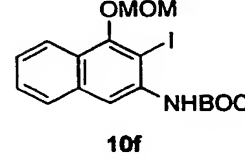
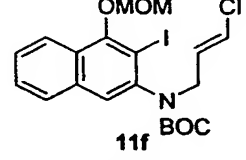
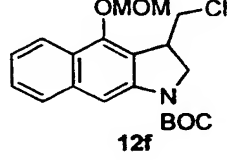
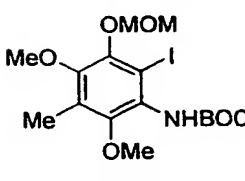
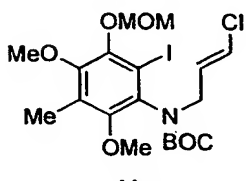
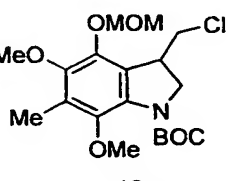
Entry	Aniline (10)	Conditions	Product (11)	Yield	Conditions	Indoline (12)	Yield
1		a		98%	c		90%
2		a		88%	c		85%
3		a		94%	c		82%
4		a		70%	d		72%
5		a		49%	d		77%
6		b		96%	c		96%
7		b		96%	c		96%

FIGURE 6

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/25992

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/84, 156, 170, 171; 548/429, 433, 469, 490, 491, 508; 585/24, 26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,598,156 A (MARTIN) 01 July 1986, Abstract and col. 1, lines 48-68; col. 2, lines 2-30.	1
Y	US 5,605,896 A (LEONARDI et al.) 25 February 1997, col. 1, lines 55-68; col. 2, lines 1-66; col. 3, lines 12-23.	11, 15
X	US 5,585,499 A (CHARI et al) 17 December 1996, col. 3, lines 39-65; col. 4, lines 1-25.	3, 9, 10, 16, 17
Y	US 5,641,780 A (AMISHIRO et al.) 24 June 1997, Abstract; col. 47, lines 1-68; col. 48, lines 1-9.	3, 15, 16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 MARCH 1999

Date of mailing of the international search report

31 MAR 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JANE C. OSWECKI

Telephone No. (703)308-1235

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/25992

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,629,430 A (TERASHIMA et al.) 13 May 1997, Abstract; col. 10, lines 1-65; col. 11, lines 1-66; col. 12, lines 1-51.	2-7, 11-13, 15-18

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/25992

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/25992

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07C 13/48, 15/04, 15/20, 15/24; C07D 209/04, 209/08, 209/18, 215/14, 215/20, 471/04, 487/02, 487/04

## A. CLASSIFICATION OF SUBJECT MATTER: US CL :

546/84, 156, 170, 171; 548/429, 433, 469, 490, 491, 508; 585/24, 26

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

### APS, CAS ONLINE

search terms: quinolin?, benzene, benzyl, naphthyl, naphthalen?, pyridin?, indolyl, indol?, benzyloxy, halo?, chloro?, iodo, amine, amino, amido, cancer, oncolog?, tumor?.

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- Group I, claims 4, 6, 7, 12, 13 and 18, drawn to optionally substituted indole and indolinone derivative compounds.
- Group II, claims 2 and 15-17, drawn to pyridyl-fused indolinone derivative compounds.
- Group III, claim 3, drawn to pyrrole-fused indolinone derivative compounds.
- Group IV, claims 5 and 11, drawn to optionally substituted benzopyridyl derivative compounds.
- Group V, claims 8-10 and 14, drawn to optionally substituted benzene and fused phenyl derivative compounds.

Claim 1 will be examined as commensurate in scope with any group elected.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: no special technical feature which makes a contribution over the prior art is common to all of the compounds in each of Groups I-V. Optionally substituted indole, indolinone, pyridine, pyrrole, benzene and fused benzene ring derivative compounds are known in the prior art. Thus, any contribution over the prior art must reside in the possibilities for the various combinations thereof, which render the compounds different from one another, as such, they are not known as equivalents in the art.